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Altered Thalamocortical Axon Morphology Following Neonatal Peripheral Nerve Damage: Implications for the Study of Developmental Neurotoxicity

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Toxicant effects on central connectivity have not been extensively characterized. Studies of developmental neurotoxicity have typically described malformations arising from damage to neuronal precursors. Toxicants may also affect later stages of neural development. In particular, they may disrupt the postnatal development of sensory systems. The purpose of this paper is to describe the effects of postnatal damage to peripheral sensory nerves on the trigeminal pathway of the rodent somatosensory system. These studies, which have demonstrated that neonatal peripheral nerve damage produces persistent alterations in central connections, have implications for the study of developmental neurotoxicology.

Organization of Somatosensory Afferent Pathways

The mystacial vibrissae on the face of the rodent are arranged in five rows, generally with five to six vibrissae in each row. The vibrissae follicles are innervated by the peripheral processes of trigeminal ganglion neurons via the infraorbital nerve whereas the central processes of the ganglion neurons project to the brainstem trigeminal complex. The efferents of the brainstem trigeminal complex project to the ventroposterior thalamus, which in turn, projects to the somatosensory neocortex.

Each of these synaptic stations in the trigeminal pathway exhibits a somatotopically organized pattern of cell and fiber clusters which mimics the pattern of vibrissae on the face (Woolsey and Van der Loos, 1970; Killackey, 1973; Killackey and Leshin, 1975; Waite 1977; Welker, 1976; Van der Loos, 1976; Belford and Killackey, 1979a; Woolsey et al., 1979; Erzurumlu et al., 1980; Arvidsson, 1982; Ma and Woolsey, 1984). While the neurons of this pathway are generated prenatally, the somatotopic pattern of clusters develops postnatally. The development of these patterns occurs centripetally, from the periphery to the more central stations, with the pattern of follicles acting as the "template" (Rice and Van der Loos 1977; Van der Loos and Dorfl, 1978; Belford and Killackey, 1979b; Jeanmonod et al., 1981).

The pattern of afferent ingrowth at each synaptic level appears to be a critical event in the development of the patterns of clustering (e.g. Rice and Van der Loos, 1977; Belford and Killackey, 1980). While the cellular mechanisms involved are not known, two kinds of interactions may contribute to this patterned ingrowth. First, axons related to the same vibrissa may cluster together as their terminal arbors develop. The pattern of neural activity, the local distribution of current, or trophic factors could provide the basis for this attraction. Second, dendrites of postsynaptic neurons are stabilized by contact with the clustered terminal arbors. This interaction results in the preferential association between a group of postsynaptic neurons and a cluster of afferents related to a single vibrissa (Harris and Woolsey, 1979; Steffen and Van der Loos, 1980). These interactions, occurring at each synaptic level, would result in the transmission of the somatotopic pattern through the pathway.

Neonatal damage to the peripheral processes of the infraorbital nerve alters the vibrissae related patterns at each synaptic level in the pathway (Van der Loos and Woolsey, 1973; Woolsey and Wann, 1976; Killackey et al., 1976; Killackey and Belford, 1979; Woolsey et al., 1979; Belford and Killackey, 1979a; Verley and Onnen, 1981; Jeanmonod et al., 1985) The development of the altered patterns also follows a centripetal direction through the pathway. When the developing peripheral processes of the infraorbital ganglion neurons are damaged, the number of neurons in the ganglion and their corresponding central projections to the brainstem trigeminal complex are

reduced (Savy et al., 1981; Waite, 1984; Jacquin and Rhoades, 1985; Bates and Killackey, 1985). The development of the altered projection to the brainstem is followed by the development of a disrupted pattern of trigemino-thalamic projections, and in turn, the development of an altered pattern of thalamocortical projections (Belford and Killackey, 1979b; Killackey and Shinder, 1979; Killackey and Belford, 1979; Bates et al., 1985). These observations of the sequential development of altered patterns supports the notion that afferent ingrowth is a critical step in the formation of somatotopic organization. The altered pattern of thalamic projections bears an intriguing relationship to the morphology of individual afferent fibers.

Altered Thalamocortical Axon Morphology

Within the face region of the rat somatosensory cortex, the anterior sinus hairs are represented by small anterolateral clusters, while the mystacial vibrissae are represented by larger posteromedial clusters (Figure 1; Welker and Woolsey, 1974). The specific thalamocortical afferents have a spatially restricted, highly branched plexus in layer IV (Lorente de No 1922, 1949). The size of the layer IV plexuses in the different cortical regions correspond to the size of the clusters (Jensen and Killackey, 1983). Fibers observed to innervate the same cluster have terminal fields which are largely coextensive while there appears to be little overlap between arbors innervating neighboring vibrissae related clusters.

In adult animals in which the infraorbital nerve is cut at birth, the overall pattern of thalamocortical projections is altered. Instead of the normal five rows of clusters, the pattern consists of elongated stripes with irregular patches (Figure 1; Jensen and Killackey, 1985). The terminal arbors are also different, ranging from compact with fairly complex branching patterns to elongated with a limited number of branches (Jensen and Killackey, 1984). The size of the layer IV plexus of these arbors may spread over three times the area seen in normal animals. As the size of the terminal arbors vary, so does the extent of overlap between adjacent arbors. The increase in the spread of terminal arbors together with the variability in the

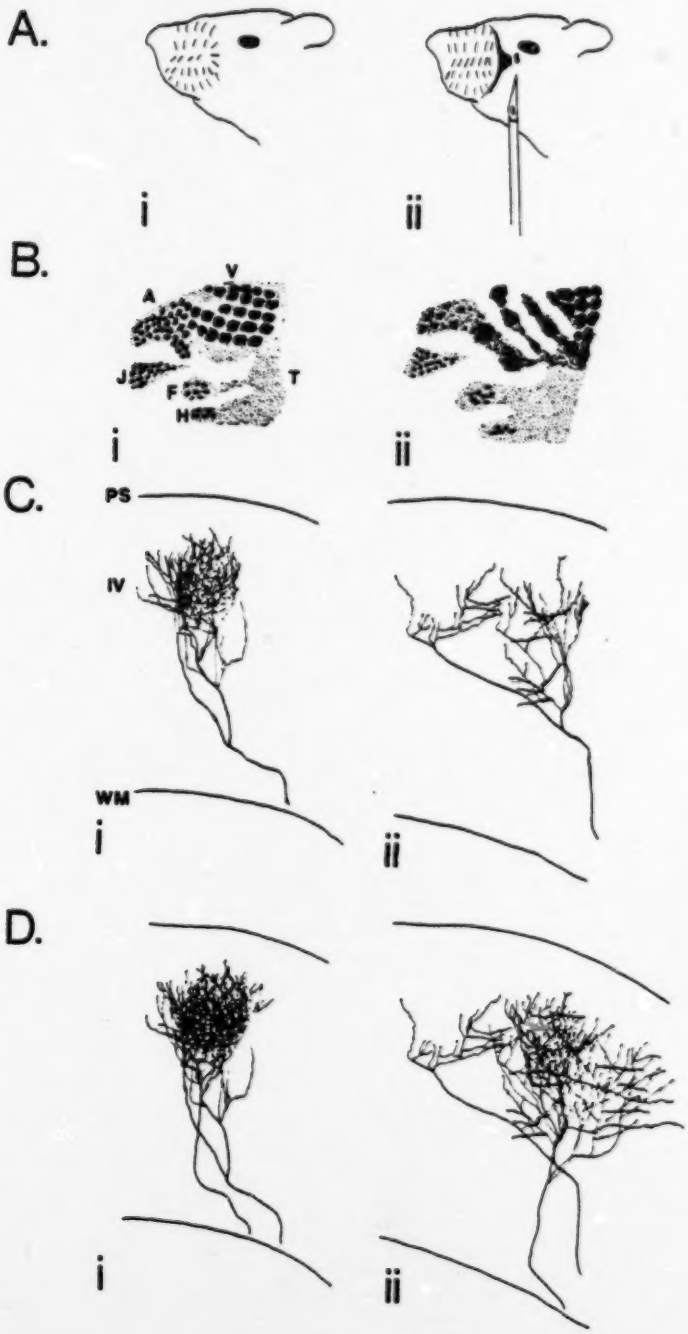
Figure 1. Diagrammatic Representation of the Effect of Neonatal Infraorbital Nerve Cut on the Adult Organization and Morphology of Thalamocortical Projections to the Rat Somatosensory Neocortex.

A. Appearance of vibrissae on the face of the rat. (i) Normal. (ii) Artistic rendering of the infraorbital nerve cut in the neonate.

B. The pattern of anterograde labeling in flattened sections of the somatosensory cortex following large injections of horseradish peroxidase in the ventroposterior thalamus. (i) The normal pattern. Stipple represents the overall projection field. Darkened areas represent the heaviest concentration of anterograde label. Letters indicate body regions within the somatosensory region: v, posterior vibrissae; a, anterior sinus hairs; j, lower jaw; f, forelimb; h, hindlimb; t, trunk. (ii) The pattern from adult animals in which the infraorbital nerve was cut at birth.

C. The morphology of terminal arbors of specific thalamocortical afferents projecting to the vibrissae region of the somatosensory neocortex as would appear reconstruction from coronal sections. (i) A terminal arbor innervating a normal vibrissa related cluster. ps, pial surface; iv, layer IV of the neocortex; wm, white matter. (ii) A terminal arbor from an adult animal in which the infraorbital nerve was cut at birth.

D. The extent of overlap of adjacent terminal arbors. (i) Coextensive overlap of two adjacent terminal arbors innervating the same vibrissae-related cluster in a normal animal. (ii) Partial overlap of two adjacent terminal arbors innervating the vibrissae region from an adult rat in which the infraorbital nerve was cut at birth.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branching characteristics accounts for the alterations in the overall pattern of thalamic projections.

Altered Functional Organization of the Neocortex

Systematic mapping of the normal somatotopic organization of rodent neocortex with microelectrode recording revealed a one-to-one relationship between a neocortical cluster and a vibrissa (Welker, 1971, 1976; Simons and Woolsey, 1979). Similar studies following infraorbital nerve damage have demonstrated several alterations in functional organization of the neocortex which correspond to observed anatomical alterations.

Peripheral nerve damage in the adult results in a different physiological organization of the neocortex than seen after nerve damage in the neonate. Peripheral damage in the adult results in "silent areas" in the neocortex, corresponding to the areas of deafferentation (Waite and Taylor, 1978; Waite 1984), indicating that the underlying circuitry is relatively stable in the adult animal. Such "silent areas" are not found in the adult cortex in animals with neonatal infraorbital nerve damage. Instead, the cortical response to stimulation within the vibrissa field is altered (Killackey et al., 1978; Waite and Taylor, 1978; Simons et al., 1984). The greater extent of alteration in the neonate is presumably related to the state of axonal and dendritic differentiation at the time of injury.

The relative topographic position of different body regions is preserved within the neocortical map of the body surface following infraorbital nerve damage (Waite and Taylor, 1978; Waite and Cragg, 1982; Waite, 1984; Simons et al., 1984). At birth, the thalamic projections present in the white matter below the developing neocortex are organized in a topographic manner (Dawson and Killackey, 1985). Neonatal peripheral nerve damage, therefore, does not alter the prenatally determined topographic organization of somatosensory neocortex.

The extent of change in the physiological organization of the vibrissae map is related to the extent of neonatal peripheral nerve damage. The effects of selectively damaging the innervation of single row of vibrissae appear to be primarily confined to the representation of the corresponding row (Killackey et al., 1978; Simons et al., 1984). In contrast, neonatal

transection of the infraorbital nerve results in a severe disruption of the entire vibrissae map (Waite and Cragg, 1982; Waite, 1984). Thus, the magnitude of peripheral nerve damage can also be reflected in extent of functional alteration in the neocortex.

Relevance to Developmental Toxic Exposure

A number of neurotoxicants are known to damage peripheral sensory neurons (e.g. Arezzo et al., 1985; Spencer and Schaumberg 1980). The experiments discussed above suggest that toxicant induced nerve damage in the neonate could produce similar changes in the neocortex. These studies also suggest several factors that are important in evaluating the effect of developmental toxic exposure on the organization of the central nervous system.

The most disruptive effects of infraorbital nerve injury on the neocortex occur as a result of damage within the first few postnatal days. In contrast, peripheral nerve damage occurring after the first postnatal week has very limited effects on the neocortex (Weller and Johnson, 1975; Woolsey and Wann 1976; Killackey and Belford, 1979; Jeamonod et al., 1981). While reinnervation of the vibrissae follicles may occur during later development (Waite and Cragg, 1979), the pattern of neocortical clusters reflects peripheral innervation present only during the first few postnatal days. Thus, transient peripheral damage can cause persistent changes in central connectivity.

The development of altered neocortical clusters corresponds to the time when thalamocortical axons are growing into the developing neocortex. Thalamocortical axons are present in the internal capsule below the neocortex on embryonic day 15 (Hicks and D'Amato, 1968). They invade presumptive layer IV of the neocortex during the first few postnatal days (Wise and Jones 1977), when synaptogenesis begins in presumptive layer IV (Kristt and Molliver 1976; Kristt, 1978). This period of synaptogenesis corresponds to the development of the somatotopic pattern of the thalamic afferents. Thus, neonatal peripheral nerve damage alters thalamic axon growth which prevents the development of normal somatotopic organization. Alterations in central connections may, therefore, occur several synapses away from the site of initial damage.

The alteration in neocortical organization also reflects the extent of damage to the peripheral nerve. In normal animals, the size of a cortical barrel is proportional to the extent of innervation of the corresponding vibrissae (Lee and Woolsey, 1977). Since the size of a layer IV plexus of a thalamic afferent corresponds to the size of a barrel, the size of this plexus is also proportional to the innervation of the corresponding vibrissa. Graded alterations in the extent of innervation of the vibrissae may therefore be reflected in graded alterations in the morphological characteristics of thalamic axons. Two such characteristics altered by neonatal peripheral damage are the complexity of the branching and the size of the layer IV plexus. Toxicant-induced alterations in the density of peripheral innervation are likely to produce similar central effects. The extent of alterations in central connections, therefore, could be related to toxicant exposure in a dose-dependent manner.

This short review has emphasized the central consequences of neonatal peripheral nerve damage. But why should a neurotoxicologist be interested in detailing central changes when peripheral nerve damage can be assessed directly? There are at least three compelling answers. First, the changes in the central structures are dramatic. They can be recognized in stained sections without magnification. Second, the central effects of neonatal peripheral damage suggest that the potential for higher order processing within the nervous system is altered. Third, while peripheral nerves may regenerate to some extent during later development, the changes in the neocortex are permanent.

In summary, transient neonatal damage to the peripheral sensory neurons alters the somatotopic organization of the neocortex. This alteration occurs two synapses away from the initial site of damage and is related to the persistent aberrant morphology of thalamocortical axons. Thus, postnatal damage to neurons which differentiate during early fetal development can produce alterations in later developing circuitry. Such alterations may represent a structural basis for the persistent functional deficits observed following many perinatal insults.

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REFERENCES

Arezzo JC, Schaumberg HH, Spencer PC. Structure and Function of the Somatosensory System: A Neurotoxicological Perspective. In: Toxicology of the Eye, Ear and Other Special Senses. Hayes AW, ed. New York, Raven Press. 1985, pp 41-54

Arvidsson J. Somatotopic organization of vibrissae afferents in the trigeminal sensory nuclei of the rat studied by transganglionic transport of HRP. J Comp Neurol 1982;211:84-92

Bates CA, Killackey HP. The organization of the neonatal rat's brainstem trigeminal complex and its role in the formation of central trigeminal patterns. J Comp Neurol 1985;240:265-287

Bates CA, Erzurumlu, RS, Killackey HP. Central correlates of peripheral pattern alterations in the trigeminal system of the rat. Dev Brain Res 1982;5:108-113

Belford GR, Killackey HP. Vibrissae representation in subcortical trigeminal centers of the neonatal rat. J Comp Neurol 1979a;183:305-322

Belford GR, Killackey HP. The development of vibrissae representation in subcortical trigeminal centers in the neonatal rat. J Comp Neurol 1979b;188:63-74

Belford GR, Killackey HP. The sensitive period in the development of the trigeminal system of the neonatal rat. J Comp Neurol 1980;193:335-350

Dawson DR, Killackey HP. Distinguishing topography and somatotopy in the thalamocortical projections of the developing rat. Dev Brain Res 1985;17:309-313

Erzurumlu RS, Bates CA, Killackey HP. Differential organization of thalamic projection cells in the

brainstem trigeminal complex of the rat. Brain Res 1980;198:427-433

Harris RM, Woolsey TA. Morphology of golgi impregnated neurons in mouse cortical barrels following vibrissae damage at different postnatal ages. Brain Res 1979;161:143-149

Hicks SP, D'Amato C. Cell migrations to the isocortex in the rat. Anat Rec 1968;160:619-634

Jacquin MF, Rhoades RH. Effects of neonatal infraorbital lesions upon central trigeminal primary afferent projections in rat and hamster. J Comp Neurol 1985;235:129-143

Jeanmonod D, Rice FL, Van der Loos H. Mouse somatosensory cortex: Alteration in the barrelfield following receptor injury at different early postnatal ages. Neuroscience 1981;8:1503-1535

Jensen KF, Killackey HP. The morphology of specific thalamocortical axons projecting to the barrel field of the rat. Soc Neurosci Abstr 1983;9(1):251

Jensen KF, Killackey HP. Infraorbital nerve section in newborn rat alters terminal arborization of thalamocortical axons projecting to SmI neocortex. Soc Neurosci Abstr 1984;10(2):1156

Jensen KF, Killackey HP. The effect of neonatal infraorbital nerve section on the pattern of thalamocortical projections to the somatosensory cortex of the adult rat. Soc Neurosci Abstr 1985;11(1):452

Killackey HP. Anatomical evidence for cortical subdivisions based on vertically discrete thalamic projections from the ventral posterior nucleus to cortical barrels in the rat. Brain Res 1973;51:326-331

Killackey HP, Belford GR. The formation of afferent patterns in the somatosensory cortex of the neonatal rat. J Comp Neurol 1979; 183: 285-304

Killackey HP, Belford GR. Central correlates of peripheral pattern alterations in the trigeminal system of the rat. Brain Res 1980;183:205-210

Killackey HP, Belford GR, Ruygo R, Ruygo DK. Anomalous organization of thalamocortical projections consequent to vibrissae removal in the newborn rat and mouse. Brain Res 1976;194:309-315

Killackey HP, Ivy GO, Cunningham TJ. Anomalous organization of SmI somatotopic map consequent to vibrissae removal in the newborn rat. Brain Res 1978;155:136-140

Killackey HP, Leshin S. The organization of specific thalamocortical projections to the posteromedial

barrel subfield of the rat somatic sensory cortex. Brain Res 1975;86:469-472

Killackey HP, Shinder A. Central correlates of peripheral pattern alterations in the trigeminal system of the rat. II. The effect of nerve section. Dev Brain Res 1981; 1:121-126

Kristt DA, Molliver ME. Synapses in newborn rat cerebral cortex: a quantitative ultrastructural study. Brain Res 1976;108:180-186

Kristt DA. Neuronal differentiation in the somatosensory cortex of the rat. I. Relationship to synaptogenesis in the first postnatal week. Brain Res 1978;150:467-486

Lee KL, Woolsey TA. A proportional relationship between peripheral innervation density and cortical neuron number in the somatosensory system of the mouse. Brain Res 1975;99:349-353

Lorente de No R. La Corteza cerebral del raton. Trab. Lab. Invest. Biol. Univ. Madr. 1922;20:1-38

Lorente de No R. Cerebral cortex:architectonics, intracortical connections. In: Physiology of the Nervous System. Fulton J, ed. Oxford, Oxford University Press. 1949, pp 274-301

Ma PM, Woolsey TA. Cytoarchitectonic correlates of the vibrissae in the medullary trigeminal complex of the mouse. Brain Res 1984;306:374-379

Rice FL, Van der Loos, H. Development of the barrels and barrel field in the somatosensory cortex of the mouse. J Comp Neurol 1977;171:545-560

Savy C, Margules S, Farkas-Bargeton E, Verley R. A morphometric study of mouse trigeminal ganglion after unilateral destruction of vibrissae follicles at birth. Brain Res 1981;217:265-277

Simons DJ, Durham D, Woolsey TA. Functional organization of mouse and rat SmI barrel cortex following vibrissal damage on different postnatal days. Somatosensory Res 1984;1:207-245

Simons DJ, Woolsey TA. Functional organization in mouse barrel cortex. Brain Res 1979;165:327-332

Spencer PS, Schaumburg HH. Classification of Neurotoxic Disease: A morphological approach. In: Experimental and Clinical Neurotoxicology Spencer P, Schaumburg H, ed. Baltimore, Williams and Wilkins. 1980, pp 92-99

Steffen H, Van der Loos. Early lesions of mouse vibrissal follicles: Their influence on dendritic orientation in the cortical barrelfield. Exp Brain Res 1980;40-419-431

Van der Loos H. Barreloids in mouse somatosensory thalamus. Neursci Lett 1976;2:1-6

Van der Loos H, Dorfl J. Does the skin tell the somatosensory cortex how to construct a map of the periphery? Neurosci Lett 1979;7:23-30

Van der Loos H, Woolsey TA. Somatosensory cortex: Structural alterations following early injury to sense organs. Science 1973;179:395-398

Verley R, Onnen I. Somatotopic organization of the tactile thalamus in normal adult and developing mice and in adult mice dewhiksered since birth. Exp Neurol 1981;72:462-474

Waite PM. Normal nerve fibers in the barrel region of developing and adult mouse cortex. J Comp Neurol 1977;173:165-174

Waite PM. Rearrangement of neuronal responses in the trigeminal system of the rat following peripheral nerve section. J Physiol 1984;352:425-445

Waite PM, Cragg BG. The effect of destroying whisker follicles in mice on the sensory nerve, the thalamo-cortical radiation and cortical barrel development. Proc R Soc Lond B 1979;204:41-55

Waite PM, Cragg BG. The peripheral and central changes resulting from cutting or crushing the afferent nerve supply to the whiskers. Proc R Soc Lond B 1982;214:191-211

Waite PM, Taylor PK. Removal of whiskers in young rat causes functional changes in cerebral cortex. Nature 1978;274:500-602

Welker C. Microelectrode delineation of fine grain somatotopic organization of SmI cerebral neocortex in albino rat. Brain Res 1971;26:259-275

Welker C. Receptive fields of barrels in the somatosensory neocortex of the rat. J Comp Neurol 1976;166:173-190

Welker C, Woolsey TA. Structure of layer IV in the somatosensory neocortex in the rat: description and comparison with the mouse. J Comp Neurol 1974;158:473-454

Weller WL, Johnson JI. Barrels in cerebral cortex altered by receptor disruption in newborn, but not five-day-od mice (Cricitdae and Muridae). Brain Res. 1975;83:504-508

Wise SP, Jones EG. Developmental studies of thalamo-cortical and commissural connection in the rat somatosensory cortex. J Comp Neurol 1978;178:187-208

Woolsey TA, Wann JR. Areal changes in mouse cortical barrels following vibrissal damage at different postnatal ages. J Comp Neurol 1976;170:53-66

Woolsey TA, Anderson JR, Wann JR, Stanfield BB. Effects of early vibrissal damage in neurons in the ventrobasal (VB) thalamus of the mouse. J Comp Neurol 1979;184:363-380

Woolsey TA, Van der Loos H. The structural organization of layer IV in the somatosensory region (SI) of the mouse cerebral cortex: The description of a cortical field composed of discrete cytoarchitectonic units. Brain Res 1970;17:205-242